Pain in the Developing World
Review

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Barriers to implementing clinical trials on nonpharmacological treatments in developing countries: lessons learnt from addressing pain in HIV

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Abstract

Pain affects over half of the people living with HIV/AIDS (LWHA), and pharmacological treatment has limited efficacy. Preliminary evidence supports nonpharmacological interventions. We previously piloted a multimodal intervention in amaXhosa women LWHA and chronic pain in South Africa with improvements seen in all outcomes, in both intervention and control groups. A multicentre, single-blind randomised controlled trial with 160 participants recruited was conducted to determine whether the multimodal peer-led intervention reduced pain in different populations of both male and female South Africans LWHA. Participants were followed up at weeks 4, 8, 12, 24, and 48 to evaluate effects on the primary outcome of pain, and on depression, self-efficacy, and health-related quality of life. We were unable to assess the efficacy of the intervention due to a 58% loss to follow-up (LTFU). Secondary analysis of the LTFU found that sociocultural factors were not predictive of LTFU. Depression, however, did associate with LTFU, with greater severity of depressive symptoms predicting LTFU at week 8 ($P = 0.01$). We were unable to evaluate the effectiveness of the intervention due to the high LTFU and the risk of retention bias. The different sociocultural context in South Africa may warrant a different approach to interventions for pain in HIV compared with resource-rich countries, including a concurrent strategy to address barriers to health care service delivery. We suggest that assessment of pain and depression need to occur simultaneously in those with pain in HIV. We suggest investigation of the effect of social inclusion on pain and depression.

Keywords: Pain, HIV/AIDS, Depression, Multimodal intervention

1. Introduction

Approximately 50% of people living with HIV/AIDS (PLWHA) have pain. This pain has been reported to affect quality of life, irrespective of pain intensity.[38] The pain may arise as a direct result of the virus and its dysregulation of the immune system, iatrogenically (treatments and procedures), as a result of complications that may arise secondary to immune failure (eg, cancer and infection), or may be incidental to the virus.[2,3,19] Moreover, more than one source of pain may coexist in a single individual.

The diversity of aetiologies and phenotypes of HIV-related pain means that it can be difficult to manage. As for all pain conditions, management should be patient-centred, integrating pharmacological and nonpharmacological treatments into multimodal interventions.[24] Regarding pharmacological treatment, the only HIV-related pain condition with high-quality evidence is painful peripheral neuropathy, and the results are far from promising.[6,9,14,37] As for nonpharmacological interventions, there is a paucity of high-quality evidence. However, disease-unrelated factors such as low education, psychological distress, and low perceived social support, all of which are amenable to nonpharmacological interventions, have been shown to contribute to the risk of HIV-related pain,[35,36] and therefore are potential targets for therapeutic interventions. Moreover, in developing

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countries such as South Africa, where financial and logistical resources constrain health care delivery, targeting these disease-unrelated risk factors with low-cost, patient-driven, and peer-led nonpharmacological interventions is an attractive and sustainable option.

Preliminary evidence supports the use of nonpharmacological treatment strategies such as exercise, education, and mindfulness for HIV-related pain.[29,30,44] Accordingly, we developed a multimodal six-week "Positive Living" programme, with components including exercise, education, and mindfulness, and tested it with 27 women living with HIV and chronic pain in an informal settlement near Cape Town, South Africa.[31] The intervention was peer-led, and all participants (intervention and control groups) received a workbook that covered the educational topics and included goal-setting worksheets. Over the 4-month period of the study, pain intensity decreased while self-efficacy and quality of life increased, in both the intervention and control groups. Given that the control group had also received the education workbook, it was possible that their improvement was due to access to educational material. An alternative possible explanation was the positive effect of being in a research study and receiving empathetic attention at scheduled data collection points. Consequently, we redesigned our protocol to address this issue directly and undertook a multisite, single-blind, randomised controlled trial to determine whether the Positive Living peer-led programme (compared to usual care, without an educational workbook) reduced pain in PLWHA. Unfortunately, the study failed; despite several strategies to support participation, participants allocated to the Positive Living intervention attended an average of less than 3 (of 6) sessions each—rendering the average treatment dose half of that intended, and loss to follow-up was too high to analyse the intended endpoint and draw a useful conclusion about the efficacy-risk profile of the intervention: 58% of randomized participants had been lost by week 8.

In this article, we report on this high loss to follow-up and provide an exploratory analysis and discussion of factors associated with the low retention. We discuss potential pitfalls for investigator-led clinical trials in developing countries.

2. Methods

2.1. Overview of the clinical trial

The aim of the trial was to determine whether the Positive Living intervention reduced pain when compared to a therapeutic relationship only, in different South African populations of PLWHA, including men and women. Secondary outcomes were depression, health-related quality of life (HRQoL), self-efficacy, and daily function. The study protocol is registered with the Pan-African Clinical Trials Registry (PACTR201410000902600) and the full protocol can be viewed at https://tinyurl.com/y7daexe9. The study was granted ethical approval by the University of Cape Town (clearance numbers: 932/2014; 890/2014; 734/2014) and the University of the Witwatersrand (clearance number: M140877).

The study was conducted at 4 sites (2 urban and 2 rural) chosen to represent diverse cultural and resource settings. The 4 sites, all of which are served by public health services, were located in: (1) Gauteng Province, at a metropolitan, multicultural antiretroviral treatment (ART) clinic in a large tertiary hospital; (2) KwaZulu-Natal Province, in a rural, resource-poor amaZulu community with a district hospital and satellite primary health care clinics; (3) Eastern Cape Province, in a rural, resource-poor amaXhosa community with a district hospital and satellite primary health care clinics; and (4) Western Cape Province, in an urban, multicultural community with a primary health care ART clinic. Each site had a site coordinator (a qualified physiotherapist or occupational therapist), a research assistant, and peer leaders. At each site, we used male or female trained research assistants and peer leaders (ie, people living with HIV) who were fluent in local languages and cultural norms.

2.1.1. Participants

Patients attending the study sites for routine HIV care were invited to participate in the study. Several methods were used to identify and recruit eligible participants. The research assistants informed individuals waiting in the HIV clinic queue about the study in their first language. Any interested participants were taken to a private research room to learn more about the study and were given the opportunity to ask questions with the research assistant in their first language. Referrals were also received for eligible patients from clinic doctors, nurses, and therapists. At the Manguzi site, prospective participants were also identified through file screening. Prospective participants were contacted telephonically, screened for eligibility, and invited to participate over the phone by a research assistant in their first language of isiZulu.

To be eligible for the study, people must have had pain of longer than 3 months' duration, be on stable HIV therapy for 6 months, and speak isiZulu/isiXhosa/Afrikaans/English as a home language. Eligible PLWHA were invited to participate in the study and told that they had an equal chance of random assignment to either of the study arms. The target of the intervention tested in this study was pain, and therefore pain severity was the primary outcome selected. A clinically meaningful improvement in pain of 3 on a 0 to 10 scale was selected as a conservative indicator of improvement as per the previous study of this intervention.[32] Based on our previous results, we calculated that a sample size of 160 would have 90% power to detect an improvement in pain of 3 points on a 0 to 10 numerical rating scale. Our previous study had a 15% attrition rate; therefore, we allowed for similar attrition in this study and aimed for a sample of 184.

2.1.2. Study design and interventions

We used a 2-arm design with patients randomised either to participate in a 6-week, peer-led multimodal intervention (Positive Living) or to receive only empathetic attention from the research assistant at each data collection point (baseline, and weeks 4, 8, 12, 24, and 48). Baseline measures were obtained by the research assistant before randomisation. Randomisation was performed by the site coordinator with a 1:1 ratio using a computer-generated random number sequence. The Positive Living intervention included a workbook for home activities, and weekly peer-led sessions for 6 weeks (openly available at: https://open.uct.ac.za/handle/11427/1004). The content of the peer-led sessions was based on information in the workbooks, and included pain education, discussions, exercise, and facilitated relaxation (the specifics of the intervention are described here[31]). The peer-led groups were for either all males or all females, and were facilitated by peer leaders of the same sex as group members to respect cultural practices and encourage open discussion of sensitive issues including health and sex. Participants in the therapeutic relationship group did not receive the workbook or attend peer-led sessions. Their only contact with the project was when they attended the clinic for assessments. However, at each of these appointments, they were seen by the same research assistant trained in optimising the therapeutic relationship. Time was allocated to allow for culturally appropriate

conversation (eg, regarding the participant's family) before study measures were completed. In these settings, this continuity in care can be regarded as an intervention because, at these clinics, patients are not seen by the same clinician at each appointment, and thus relational continuity is lacking. The peer-led groups also experienced the same care at their follow-up assessments.

2.1.3. Outcomes

The primary outcome of the study was pain severity assessed using the Pain Severity Subscale of the Brief Pain Inventory (BPI) (which takes a mean of participant ratings of worst, least, average, and current pain on a 0–10 numerical rating scale at all sites except Johannesburg. The Johannesburg isiZulu speakers did not report "average" pain,[27] and so the mean of worst, average, and current was taken) at 6 months compared with baseline values. The BPI is validated for use in South African English, isiZulu, and isiXhosa, and an Afrikaans version is available.[27,33,34] In addition to pain severity, pain interference with function was assessed using the Pain Interference Subscale of the BPI, which provides a mean of participant ratings of pain-related interference with 7 domains of daily function. Depression was assessed using the validated Beck Depression Inventory.[35] Self-efficacy in managing chronic disease, that is, a person's confidence in managing their chronic disease, was assessed using the Chronic Disease 6-item self-efficacy scale (SE-6).[23] The SE-6 was developed to test the efficacy of chronic disease education programmes and has also been found to be a valid and reliable method of measuring self-efficacy in chronic conditions[23] including HIV.[11,12] The SE-6 covers the dimensions of symptom control, role function, emotional functioning, and communication with physicians. Health-related quality of life was assessed with the Euroquol-5D (EQ-5D)[36] (validated in a South African population, used in HIV cohorts and available in all 4 languages[38]). A sociodemographic questionnaire was used to record the demographic characteristics of all participants, and included: highest level of education, employment, and current medical history (including stage of HIV, latest $CD4^+$ T-cell count, and current HIV management). In addition, we used the SOS mnemonic[18] to evaluate health literacy because educational level alone is not an adequate proxy for level of health-related literacy.[18]

2.1.4. Participant retention strategies

All participants were provided with an appointment card listing the assessment dates, and dates of the peer-led sessions (in the Positive Living intervention group only). Multiple phone numbers were recorded for each participant, including the phone number of a trusted family member or friend, and every participant was sent short messenger service reminders of every appointment. If participants missed an appointment, care was fostered through telephonic appointment reminders, and by the research assistant gently and kindly asking for reasons when participants were unable to attend. Every participant was reimbursed for transport expenses, provided with mobile phone airtime, and given a healthy snack at each visit. Gratitude for the participant's involvement was expressed at every visit.

2.2. Statistical analysis

Attempts to analyse the primary or secondary outcome measures were flawed because of the high loss to follow-up (Supplement 4, available at http://links.lww.com/PR9/A57). We have described the rate of loss to follow-up and undertaken an exploratory analysis of variables collected at baseline that were associated with loss to follow-up. Preliminary assessment of the data showed similar trends across the 4 study sites in the proportion of participants lost to follow-up at each data collection time point (Supplement 1, available at http://links.lww.com/PR9/A57); so, we collapsed the data across the study sites, and analysed the pooled data. All supplementary material and analysis scripts can be accessed at figshare Fileset: https://doi.org/10.6084/m9.figshare.7654637.v1 and http://links.lww.com/PR9/A57 (Kamerman Peter; Madden Tory; Parker Romy; Devan Dershnee; Cameron Sarah; Jackson Kirsty; et al. [2019]: Analysis scripts and supplementary files: Barriers to implementing clinical trials on non-pharmacological treatments in developing countries—lessons learnt from addressing pain in HIV).

We classified participants as being lost to follow-up after being uncontactable for 2 or more follow-up appointments (or week 48 was reached), with the time of loss to follow-up being taken as the last time point for which data were available. To accommodate erratic attendance at the baseline assessment and subsequent reassessment at later time points, we extended our "lost to follow-up" classification to include the following: (1) participants who consented to take part, but failed to attend the baseline (week 0) and week 8 assessments were classified as being lost to follow-up before week 0, irrespective of whether they returned for assessment at other time points; and (2) participants who missed the baseline assessment but were assessed at week 8 were classified as lost to follow-up if they missed 2 or more assessments after week 8. The time of their loss to follow-up (LTFU) was considered to be the last time point for which data were available.

Our exploratory analysis of baseline factors that were associated with being lost to follow-up was focussed on 4 variables: sex, employment/income stability, anxiety and depression, and study group allocation. Sex,[49] employment,[1] and depression[8] may be associated with differential use of health care services, and group allocation speaks to the possibility that participants may have withdrawn from the study due to dissatisfaction with their group allocation (for any reason). We limited our analysis to only 4 variables and univariate tests because of the exploratory nature of the analysis. Fisher exact test was used to assess the relationship between loss to follow-up and sex, employment, and group allocation. The relationship between loss to follow-up and depression was assessed using logistic regression with severity of depression coded as an ordinal variable (severity of depression rated as none, mild, moderate, or severe based on published criteria for the Beck Depression Inventory).[42] Because we observed participant dropout throughout the study period, we chose a single point in time (week 8) at which to assess the relationship between loss to follow-up and each of the 4 variables. We chose week 8 because it was the earliest assessment time point after completion of the 6-week Positive Living programme. All analyses were performed using R version 3.5.2,[39] and the analysis scripts can be downloaded from https://github.com/kamermanpr/HIP-study.git.

3. Results

3.1. Description of the cohort

We recruited 162 participants (descriptive statistics of the cohort at each study site are presented in Supplement 1, available at http://links.lww.com/PR9/A57) whose sociodemographic profiles resembled the population served by each clinic (**Table 1**). The recruited participants had been on ART for a median of 3 years, and most were on first-line ART (stavudine + lamivudine + efavirenz/nevirapine). Brief Pain Inventory scores were interpreted as mild (<4), moderate (4–7), and severe (>7).[48] On average, participants reported moderate pain on the Pain

Table 1

Characteristics of the cohort (n = 160).

	Full sample (n = 160)	By sex	
		Female (n = 97)	Male (n = 63)
Demographics			
Age in years (mean [SD])	35.2 (5.7)	34.2 (6.0)	36.8 (4.8)
Education category (n [%])			
0–7 years	44 (28)	26 (16)	18 (11)
8–12 years	112 (71)	68 (43)	44 (28)
More than 12 years	2 (1)	2 (1)	0 (0)
Employment status			
Employed	51 (41)	26 (38)	25 (45)
Student/volunteer	2 (2)	2 (3)	0 (0)
Unemployed	64 (51)	38 (55)	26 (46)
Unable to work; disability grant	8 (6)	3 (4)	5 (9)
SOS Mnemonic = LHL (n [%])	78 (69)	59 (76)	19 (24)
HIV management			
Years on ART (median [IQR])	3 (1–5)	3 (1–5)	4 (2–5)
HIV management (n [%])			
First-line ART	115 (74)	65 (42)	50 (32)
Second-line ART	36 (23)	24 (15)	12 (8)
No ART	5 (3)	5 (3)	0 (0)
CD4 T-cell count (cells/μL) (median [IQR])	376 (225–547)	411 (245–571)	335 (211–492)
Study outcomes			
Pain severity (median [IQR])	5 (4–6)	5 (4–6)	5 (4–6)
Pain interference (median [IQR])	5 (3–7)	5 (4–7)	5 (2–7)
Depression (median [IQR])	21 (13–31)	26 (17–33)	16 (10–25)
Self-efficacy (median [IQR])	7 (5–9)	8 (5–9)	7 (6–9)
HRQOL* VAS (median [IQR])	60 (50–76)	60 (50–75)	70 (50–80)
HRQOL* index (median [IQR])	0.69 (0.49–0.76)	0.66 (0.47–0.76)	0.73 (0.51–0.76)

Education categories broadly divide schooling as per the South African system, in which 0 to 7 years is primary education, 8 to 12 years is secondary education, and >12 years is tertiary education. Percentage data are based on the cases for which data were available. For example, 28% of cases with education data available (n = 158) had 0 to 7 years of education; 16% of cases with data available were female with 0 to 7 years of education.

* HRQoL, Health-related quality of life, measured on EQ5D-3L.

ART, antiretroviral treatment; IQR, interquartile range; LHL, low health literacy.

Severity Score of the BPI (4/10) and moderate Pain Interference (5/10). Although they reported good self-efficacy (8/10), their HRQoL was interpreted as low (60/100), similar to those of South Africans living with disabilities.[17] In addition, mean BDI scores for the cohort were 21, which is in the depressed range.[4]

3.2. Treatment dosage

Participant attendance decreased in both the therapeutic relationship (n = 72) and the positive living (n = 88) groups (**Fig. 1**). Session attendance data were available from 3 of the 4 sites. In participants allocated to receive the Positive Living intervention, session attendance was highly variable, with participants attending an average of 2.8 of the 6 sessions offered.

3.3. Loss to follow-up

Figure 2 shows the percentage of participants from the original cohort (n = 160) retained at each study visit. Participant attrition occurred fairly steadily for the duration of the study, with 12 participants lost to follow-up between consent and baseline (week 0), 26 participants between weeks 0 and 4, 20 participants between weeks 4 and 8, 7 participants between weeks 8 and 12, and 20 participants between weeks 24 and 48. In total, 93 of the original 160 people (58%) who consented to take part in the study were lost to follow-up.

We were unable to assess efficacy of the intervention on any of the study outcome measures due to a 58% loss to follow-up at week 48 (LTFU). We defined LTFU as a participant being uncontactable for 2 or more follow-up assessments.

3.3.1. Exploratory analysis

We found no association between loss to follow-up and employment/income stability {stable income = employed or in receipt of a social grant at baseline; Fisher exact test: odds ratio (95% confidence interval [CI]) = 1.4 (0.7–3.1), $P = 0.309$}, sex (Fisher exact test: odds ratio [95% CI] = 0.9 [0.4–1.9], $P = 0.867$), and group allocation (Fisher exact test: odds ratio [95% CI] = 0.7 [0.4–1.4], $P = 0.0.326$). Exploratory visualisation of the relationship between the number of sessions attended by participants in the Positive Living group and change in pain reported from week 0 to week 48 showed no relationship. However, for depressive symptoms, we found a significant positive relationship between the severity of depression and loss to follow-up (**Fig. 3**; logistic regression main effect: type II sum of squares analysis of deviance $\chi^2_{(3)} = 11.4$, $P = 0.01$; odds ratio for the linear component of orthogonal polynomial contracts [95% CI] = 4.1 [1.7–11.8], $P = 0.003$; see Supplement 3 for details of the cubic and quadratic contrasts, available at http://links.lww.com/PR9/A57).

4. Discussion

This study aimed to assess the efficacy of the Positive Living peer-led exercise and education intervention for reducing pain in both male and female PLWHA in South Africa. However, we were unable to determine the efficacy of the intervention due to very high LTFU. The high LTFU was unexpected because multiple strategies (described in Methods) had been used to optimise participation[20,50] and the initial study of effectiveness in a discreet South African population had only a 15% LTFU over 16 weeks.[32] By contrast, 36% of the current cohort had been lost by week 8,

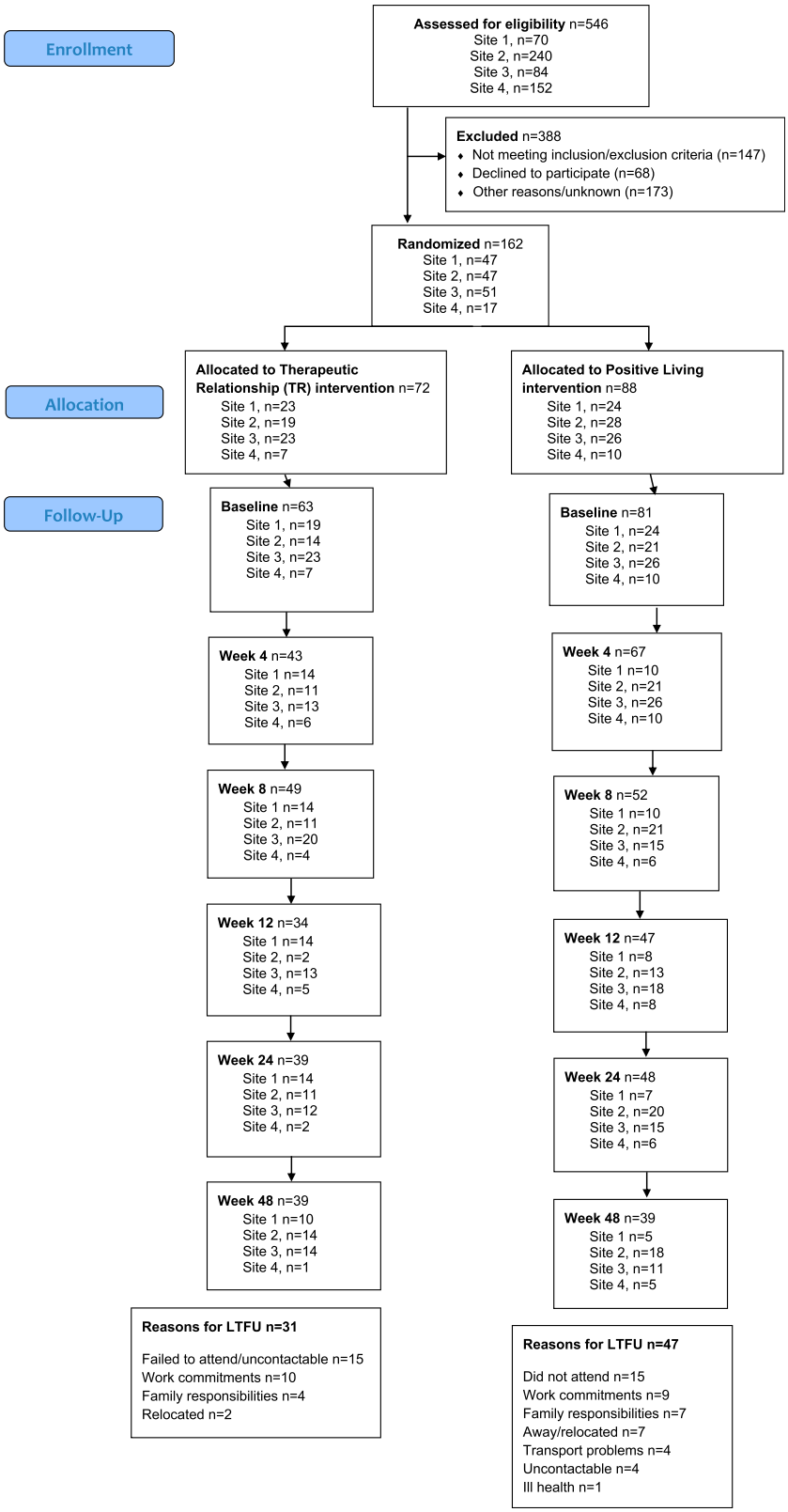

Figure 1. CONSORT flow diagram of recruitment, participation, and follow-up attendance. LTFU, loss to follow-up.

and 41% by week 12. Exploratory analysis of factors hypothesised to predict LTFU showed that employment/income stability, sex, or group allocation did not relate to LTFU. Importantly, the severity of depressive symptoms at baseline did predict dropout at 8 weeks. We believe our results raise important considerations for the design of clinical trials of nonpharmacological interventions in developing countries.

The LTFU seen here contrasts with good retention seen in preliminary studies of nonpharmacological interventions for pain in PLWHA in the United States.[26,45] Our high loss to follow-up

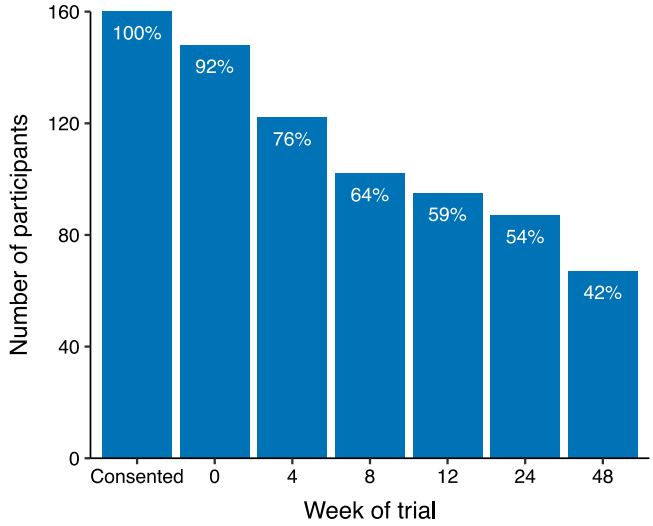

Figure 2. Number of participants (and percentage of the initial cohort) retained in the study from recruitment to week 48 (160 participants consented to take part in the study). Participants were classified as "lost to follow-up" if they had 2 or more successive time points with missing data (or week 48 was reached), with the time of loss to follow-up being taken as the last time point for which data were available. To accommodate erratic attendance at the baseline assessment (week 0) and subsequent reassessment time points, we extended our "lost to follow-up" classification to include: (1) participants who were recruited, but failed to attend assessments at week 0 (baseline) and week 8 (a key time point for assessing the efficacy of the intervention) were classified as being "lost to follow-up" from week 0 irrespective of whether they were assessed at other time points; and (2) participants who missed the baseline assessment, but who were reassessed at week 8 were classified as "lost to follow-up" according to the 2 or more successive time points with missing data rule, but starting at week 8.

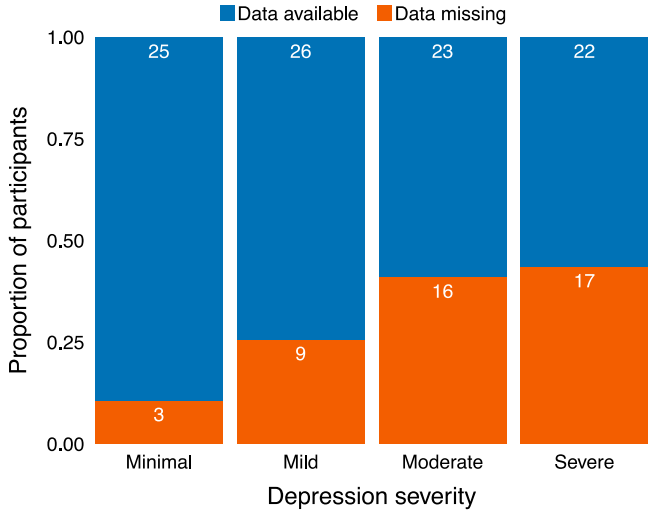

Figure 3. Relationship between severity of depressive symptoms at week 0 (baseline), as rated on the Beck Depression Inventory (BDI), and availability of data at week 8 (a key time point for assessing the efficacy of the intervention that was used to define "loss to follow-up," Fig. 1) (n = 141). One study site used the original version of the BDI (BDI-I), and scores from the questionnaire were partitioned into minimal, mild, moderate, and severe categories as follows: 0 to 9 = minimal depression, 10 to 18 = mild depression, 19 to 29 = moderate depression, and 30 to 63 = severe depression.[44] Three study sites used the 1996 update of the BDI (BDI-II), and scores from the questionnaire were partitioned into categories as follows: 0 to 13 = minimal depression, 14 to 19 = mild depression, 20 to 28 = moderate depression, and 29 to 63 = severe depression.[45]

suggests that management of pain may be a lower priority for South African PLWHA than for PLWHA in the United States. Indeed, our approach to the exploratory analysis of the high LTFU was based on a recent study that highlighted the role of the social determinants of health, suggesting that sociocultural or economic factors may be more pressing concerns than chronic pain for PLWHA who have pain.[47] In urban South African PLWHA, those with chronic pain report more economic stress (worries about money and access to food) and social stress (worries about family) than those without chronic pain.[47] In a developing country where poverty is a reality (national unemployment is 25% officially and 40% unofficially[41]), income stability is uncommon in those using public health care, and social stressors and mental health disorders have been described as pervasive.[10,16] In such contexts, coping with poverty may be prioritised over management of health.

The association between severity of depression and LTFU was clear in the current data. The high prevalence of depression in the study was not surprising, given that 1 in 10 South Africans will have at least one episode of depression during their lifetime.[43] Reduced motivation and social withdrawal as a consequence of depressive symptoms may have been the reason for LTFU. We were not able to analyse the efficacy of either arm of the intervention, but it is possible that those with greater depressive symptoms may have been less likely to benefit from either the intervention or from the relational continuity in the usual care group.

Considering that depression is associated with greater symptomatology in PLWHA[5] and that greater depressive symptoms have been associated with poor adherence to ART,[40] we suggest that integrating routine mental health assessment into normal HIV care (which is currently not the case in South Africa or many other developing countries) may be beneficial. Given the intertwined nature of depression and pain,[22] assessment and treatment of both should occur in unison. To address pain and depression simultaneously could yield symbiotic benefit as addressing pain improves depression, and improving depression improves pain. There is evidence from well-resourced settings that pain and depression can both be improved by interdisciplinary, psychologically informed pain management programs.[7,21] The challenge in the South African setting, informed by this study, is in motivating moderate to severely depressed pain patients to remain in the study or to continue in the intervention and not drop out. Multimodal interdisciplinary assessment and treatment strategies could empower PLWHA to manage both pain and depression. Furthermore, trials involving PLWHA ought to consider assessing depressive symptoms. Indeed, any study in which LTFU is predicted by depression risks overestimating treatment efficacy if the data from participants who are LTFU are not carried forward in analysis.

The symptoms that continue to plague PLWHA, including pain, may reflect the social determinants of health and poverty (eg, low levels of education and unstable income). Our results did not support the hypothesis that LTFU was due to sociocultural or economic factors; however, it is possible that the lack of association between these markers of socioeconomic status and LTFU may conceal a strain for survival in the entire cohort regardless of relative status. Anecdotally, many of our participants may live below or close to the poverty line [Statistics South Africa defined the South African poverty line at ZAR1138 ($95) per person per month in 2017[32]. A "disability" social grant provided ZAR1600 ($134) per month in 2017. Beneficiaries are forbidden from seeking formal employment[30]]. Many PLWHA have unstable income, like those described here.

In the developing countries that are home to the majority of PLWHA, social support grants are uncommon and may be no more common in those with pain compared to those without (5% of each group).[25,50] Although a South African disability grant clears the poverty line, it is commonly used to support an entire household rather than only the grantee, and our "employed" category included those working on a casual or erratic basis. Even the nuances of employment conditions may have different influences on participant retention. Participants who were unemployed may have become LTFU due to internal movement between rural and urban areas to access economic opportunity and employment.[46] Such "internal migration" is undertaken by more than 10% of South Africans each year. By contrast, for those who were employed, employers may have made it difficult to attend. Indeed, some participants reported that their employers were unwilling to accept medical notes and penalised employees by withholding wages for time spent at clinic visits. The age of ART has shifted the treatment strategy for PLWHA towards optimising quality of life, but our experience suggests that progress towards optimising quality of life may only be possible in the presence of a concurrent strategy to address the many barriers to health care service delivery that affect this population.

We used several strategies that have been described elsewhere as improving study compliance.[50] Participants in this study were reimbursed for travel costs but not for time. One male participant from one of the rural sites explained why he could not attend a follow-up appointment, saying:

> "I don't have time for things which do not give me money. I cannot leave my job and come for something which is not going to give me money."

One solution may be to increase participant reimbursement so that it is equivalent to any income that participants may miss out on due to participation. However, the value of such a strategy is questionable. Increasing reimbursement may help participation and retention in research studies such that an intervention can actually be tested but could result in testing of interventions that are not realistic for patients to undertake. Furthermore, in a population struggling with poverty, the "effectiveness" of the intervention as demonstrated by such a study could actually depend on the temporary financial security linked to the retention strategy, rather than on the intervention itself.

Offering interventions out of work hours could improve participation and retention.[20] We did offer the intervention on the weekend at one site, but this did not improve attendance—perhaps because work hours in the informal sector are unregulated and unpredictable.[15] Another strategy could be to offer the intervention through technology—for example, as a download to a mobile phone. However, that is not realistic in South Africa: although about 30% of the population owns a smartphone, data are more expensive than elsewhere in Africa and the world [Data prices in South Africa are the most expensive in Africa at USD7.60/gigabyte], and Wi-Fi is not freely available.[13] Furthermore, many patients lack access to electricity, and it is not uncommon to see patients arriving at clinics and plugging their phones in to charge while they wait to be seen. Given the challenges of connectivity and electricity, interventions that rely on technology of this kind are not currently feasible.

Our results could seem bleak in that the socioeconomic and mental health landscape in South Africa may not be conducive to clinical trialling, let alone clinical provision, of nonpharmacological interventions for pain in HIV. However, all is not lost: previous studies in resource-poor settings have found that, for PLWHA who do participate in studies, participation alone seems to improve their pain, depression, and QOL.[28,32] This improvement-through-participation effect requires verification and the mechanisms need to be explored. It may be that social inclusion, such as being part of a research study, is a powerful antidote to the stress of being poor and living with both HIV and pain. This line of inquiry could lead to simple, cost-effective interventions that use social inclusion strategies to simultaneously address pain and depression, thus improving HRQoL in PLWHA and doing so at low cost. It remains a priority to address pain and HRQoL in PLWHA who carry the additional burdens of poverty and mental health problems, and social inclusion may be a promising approach.

Disclosures

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A57.

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